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(54) Title: 32 HUMAN SECRETED PROTEINS

(57) Abstract: The present invention relates to novel human secreted proteins and isolated nucleic acids containing the coding regions of the genes encoding such proteins. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human secreted proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating diseases, disorders, and/or conditions related to these novel human secreted proteins.

cancers of the pancreas (e.g. diabetes mellitus), adrenal cortex, ovaries, pituitary (e.g., hyper-, hypopituitarism), thyroid (e.g. hyper-, hypothyroidism), parathyroid (e.g. hyper-,hypoparathyroidism) , hypothallamus, and testes. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:39 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 497 of SEQ ID NO:39, b is an integer of 15 to 511, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:39, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 30

The translation product of this gene shares sequence homology with apolipoprotein A-IV (see, e.g., Genbank Accession Nos. emb|CAA11020.1| (AJ222966) and gb|AAA35379.1|; all references available through these accessions are hereby incorporated in their entirety by reference herein). (Genbank Accession Nos. emb CAA11020.1 polypeptide sequence:

MFLKAVVLSLALVAVTGARAEVNADQVATVMWDYFSQLGSNAKKAVEHLQ
KSELTQQLNTLFQDKLGEVNTYTEDLQKKLVPFATELHERLTKDSEKLKEEIR
RELEELRARLLPHATEVSQKIGDNVRELQQRLGPFTGGLRTQVNTQVQQLQR
QLKPYAERMESVLRQNIRNLEASVAPYADEFKAKIDQNVEELKGSLTPYAEEL
KAKIDQNVEELRRSLAPYAQDVQEKLNHQLEGLAFQMKKQAEELKAKISAN
ADELRQKLVPVAENVHGHLKGNTEGLQKSLLELRSHLDQQVEEFRLKVEPYG
ETFNKALVQQVEDLRQKLGPLAGDVEGHLSFLEKDLRDKVNTFFSTLKEEAS

QGQSQALPAQEKAQAPLEG (SEQ ID NO: 206). Genbank Accession Nos. gb AAA35379.1:

MFLKAVVLTLALVAVAGARAEVSADQVATVMWDYFSQLSNNAKEAVEHLQ
KSELTQQLNALFQDKLGEVNTYAGDLQKKLVPFATELHERLAKDSEKLKEEI
GKELEELRARLLPHANEVSQKIGDNLRELQQRLEPYADQLRTQVNTQAEQLR
RQLDPLAQRMERVLRENADSLQASLRPHADELKAKIDQNVEELKGRLTPYAD
EFKVKIDQTVEELRRSLAPYAQDTQEKLNHQLEGLTFQMKKNAEELKARISA
SAEELRQRLAPLAEDVRGNLKGNTEGLQKSLAELGGHLDQQVEEFRRRVEPY
GENFNKALVQQMEQLRQKLGPHAGDVEGHLSFLEKDLRDKVNSFFSTFKEKE
SQDKTLSLPELEQQQEQQQEQQQEQVQMLAPLES (SEQ ID NO: 207). Genbank Accession No. gb AAA37214.1:

MFLKAAVLTLALVAITGTRAEVTSDQVANVVWDYFTQLSNNAKEAVEQFQK
TDVTQQLSTLFQDKLGDASTYADGVHNKLVPFVVQLSGHLAKETERVKEEIK
KELEDLRDRMMPHANKVTQTFGENMQKLQEHLKPYAVDLQDQINTQTQEM
KLQLTPYIQRMQTTIKENVDNLHTSMMPLATNLKDKFNRNMEELKGHLTPRA
NELKATIDQNLEDLRRSLAPLTVGVQEKLNHQMEGLAFQMKKNAEELQTKV
SAKIDQLQKNLAPLVEDVQSKVKGNTEGLQKSLEDLNRQLEQQVEEFRRTVE
PMGEMFNKALVQQLEQFRQQLGPNSGEVESHLSFLEKSLREKVNSFMSTLEK
KGSPDQPQALPLPEQAQEQAQEQVQPKPLES (SEQ ID NO: 208).).

This invention relates to newly identified Apolipoprotein polynucleotides, polypeptides encoded by such polynucleotides, the use of such polynucleotides and polypeptides, as well as the production of such polynucleotides and polypeptides. The polypeptide of the present invention has been putatively identified as a human apolipoprotein A-IV homolog derived from a normal human liver cDNA library, sometimes hereafter referred to as "Apolipoprotein A-IV-Like" and/or "ApoA-IV-L". The invention also relates to inhibiting the action of such polypeptides.

Apolipoproteins are protein constituents of plasma lipid transport particles. ApoA-IV is associated with triglyceride-rich lipoproteins and HDL, and also occurs in a lipoprotein-free form. It has been proposed to play a role in reverse cholesterol transport on the basis of in vitro properties. It has been demonstrated that apoA-IV can bind to hepatocytes. Since it appears that the expression of our homolog, apoA-IV-L, is liver-enriched, if not liver-specific, perhaps there is some "hand-off"

mechanism, whereby HDL/cholesterol is transported to the liver by apoA-IV and transferred to apoA-IV-L for elimination from the liver. Therefore, apoA-IV-L is intimately involved in cholesterol metabolism, cholesterol transport, and removal of cholesterol from the body. The ApoA-IV protein has also been attributed to regulating food-intake (J Nutr. 1999 Aug;129(8):1503-6).

In transgenic mice that are expressing apoA-IV in the liver, it appears that apoA-IV can protect against atherosclerosis by a mechanism that does not involve an increase in HDL cholesterol concentration. Therefore, perhaps our homolog, apoA-IV-L can also provide protection against atherosclerosis.

Studies have demonstrated that dietary fat clearance is modulated by genetic variation in the apolipoprotein A-IV gene locus. For example, the A-IV-347Ser polymorphism is associated with the variability in low density lipoprotein (LDL)-cholesterol response to dietary therapy. A putative polymorphism has been specifically identified within the present invention (a serine to isoleucine polymorphism at amino acid residue 258 of Figures 7A-B (amino acid residue 258 of SEQ ID NO: 212). Perhaps this possible polymorphism, or others as yet undetected in the gene locus for apoA-IV-L may likewise provide a diagnostic for altered lipid/cholesterol/bile metabolism.

Interestingly, other apolipoproteins, specifically apolipoprotein(a) ("apo(a)") is a recognized cardiovascular risk factor. Apo(a) is characterized by a high genetic polymorphism with at least 34 isoforms in plasma. Recent studies have shown that in atherothrombosis apo(a) polymorphism could play a role independent of Lp(a) levels. In particular, apo(a) phenotypes seem to have their highest predictive value for coronary heart disease, when apo(a) isoforms are detected by high resolution phenotyping methods and when an adequate operative cut-off of apo(a) polymorphism is used. A strong association between apo(a) phenotypes and coronary heart disease has been also found in hypertensive, diabetic, and uremic patients. Moreover, apo(a) phenotypes seem to correlate well with the severity of coronary atherosclerosis and the age of clinical onset of coronary heart disease. These studies suggest that apo(a) polymorphism may have a great clinical usefulness in a primary prevention setting, since apo(a) phenotypes could be used together with Lp(a) levels as strong genetic

predictors of atherothrombosis. The analysis of apo(a) polymorphism appears to be particularly useful in healthy subjects with a family history of atherothrombotic diseases, in patients with diseases at high cardiovascular risk (diabetes, hypertension, hypercholesterolemia) and in subjects with conditions modifying Lp(a) levels (Cardiologia. 1999 Apr;44(4):347-54, and Am J Cardiol. 1999 May 13;83(9B):3F-12F). Thus, it is anticipated that at the present apolipoprotein A-IV-like protein, and/or polymorphisms thereof, may portray similar clinical phenotypes, whose expression levels may also serve as a diagnostic for cardiovascular diseases and/or disorders, if not also for liver diseases and/or disorders.

The polypeptide of the present invention has been putatively identified as a member of the apolipoprotein family and has been termed Apolipoprotein A-IV-Like protein ("ApoA-IV-L"). This identification has been made as a result of amino acid sequence homology to the apolipoprotein A-IV of Sus scrofa (emb|CAA11020.1), the human apolipoprotein A-IV (gb|AAA51744.1), and the mouse apolipoprotein A-IV (gb|AAA37214.1).

Figures 7A-B show the nucleotide (SEQ ID NO: 40) and deduced amino acid sequence (SEQ ID NO: 212) of ApoA-IV-L. Predicted amino acids from about 1 to about 23 constitute the predicted signal sequence (amino acid residues from about 1 to about 23 in SEQ ID NO: 212) and are represented by the underlined amino acid regions; and nucleic acid residues from about 781 to about 885 (nucleic acid residues from about 781 to about 885 in SEQ ID NO:212 which contitutes the putative polymorphism domain as is represented by the double underlined nucleic acids; and amino acid 258 which constitutes a putative Serine to Isoleucine polymorphism (amino acid residue 258 in SEQ ID NO155 and is represented by the bold amino acid.

Figure 8A-8B shows the regions of similarity between the amino acid sequences of the Apolipoprotein A-IV-Like (ApoA-IV-L) protein (SEQ ID NO:212) the apolipoprotein A-IV of Sus scrofa (SEQ ID NO: 206), the human apolipoprotein A-IV (SEQ ID NO: 207), and the mouse apolipoprotein A-IV (SEQ ID NO: 208).

Figure 9 shows an analysis of the Apolipoprotein A-IV-Like (ApoA-IV-L) amino acid sequence. Alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity; amphipathic regions; flexible regions; antigenic index and surface probability are shown.

A polynucleotide encoding a polypeptide of the present invention is obtained from human normal liver, hepatoma, and pancreas tumor tissues. The polynucleotide of this invention was discovered in a human normal liver cDNA library. As shown in Figures 7A-B and Figure 8, ApoA-IV-L has strong conservation between other members of the apolipoprotein A-IV family. The polynucleotide contains an open reading frame encoding the full-length apolipoprotein A-IV polypeptide of 366 amino acids, and a predicted molecular weight of 41.237 kilodaltons. ApoA-IV-L exhibits a high degree of homology at the amino acid level to the the apolipoprotein A-IV of Sus scrofa, the human apolipoprotein A-IV, and the mouse apolipoprotein A-IV (as shown in Figure 8).

The present invention provides isolated nucleic acid molecules comprising a polynucleotide encoding the ApoA-IV-L polypeptide having the amino acid sequence shown in Figures 7A-B (SEQ ID NO: 212). The nucleotide sequence shown in Figures 7A-B (SEQ ID NO: 40) was obtained by sequencing a cDNA gene (HLDRR08), which was deposited on September 27, 1999 at the American Type Culture Collection, and given Accession Number PTA-796. The deposited gene (HLDRR08) is inserted in the pCMV Sport 3.0 plasmid (Life Technologies, Rockville, MD) using the SalI/NotI restriction endonuclease cleavage sites.

The present invention is further directed to fragments of the isolated nucleic acid molecules described herein. By a fragment of an isolated DNA molecule having the nucleotide sequence of the deposited cDNA or the nucleotide sequence shown in SEQ ID NO: 40 is intended DNA fragments at least about 15nt, and more preferably at least about 20 nt, still more preferably at least about 30 nt, and even more preferably, at least about 40 nt in length which are useful as diagnostic probes and primers as discussed herein. Of course, larger fragments 50-1500 nt in length are also useful according to the present invention, as are fragments corresponding to most, if not all, of the nucleotide sequence of the deposited cDNA or as shown in SEQ ID NO: 40. By a fragment at least 20 nt in length, for example, is intended fragments which include 20 or more contiguous bases from the nucleotide sequence of the deposited cDNA or the nucleotide sequence as shown in SEQ ID NO: 40. In this context "about" includes the particularly recited size, larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini.

Representative examples of ApoA-IV-L polynucleotide fragments of the invention include, for example, fragments that comprise, or

Alternatively, consist of, a sequence from about nucleotide 1 to about 50, from about 51 to about 100, from about 101 to about 150, from about 151 to about 200, from about 201 to about 250, from about 251 to about 300, from about 301 to about 350, from about 351 to about 400, from about 401 to about 450, from about 451 to about 500, from about 501 to about 550, from about 551 to about 600, from about 601 to about 650, from about 651 to about 700, from about 701 to about 750, from about 751 to about 800, from about 801 to about 850, from about 851 to about 900, from about 901 to about 950, from about 951 to about 1000, from about 1001 to about 1050, from about 1051 to about 1100, from about 1101 to about 1150, from about 1151 to about 1200, from about 1201 to about 1250, from about 1251 to about 1300, from about 1301 to about 1350, from about 1351 to about 1393, from about 64 to about 129, from about 67 to about 1161, and from about 130 to about 1161 of SEQ ID NO: 40 (Figures 7A-B), or the complementary strand thereto, or the cDNA contained in the deposited gene. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini.

Alternatively, consisting of, the predicted mature apolipoprotein A-IV-L (amino acid residues from about 24 to about 366 in Figures 7A-B (amino acids from about 24 to about 366 in SEQ ID NO: 212); the full-length apolipoprotein A-IV-L (amino acid residues from about 1 to about 366 in Figures 7A-B (amino acid residues from about 1 to about 366 in SEQ ID NO: 212); the full-length apolipoprotein A-IV-L minus the start methionin (amino acid residues from about 2 to about 366 in Figures 7A-B (amino acid residues from about 2 to about 366 in SEQ ID NO: 212). In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini.

Alternatively, consist of, the putative polymorphic domain, and specifically polynucleotide fragments having a sequence from about nucleotide 825 to about 846, from about 822 to about 849, from about 820 to about 852, from about 817 to about 855, from about 814 to about 858, from about 811 to about 861, from about 808 to about 864, from about 805 to about 867, from about 802 to about 870, from about 799

to about 873, from about 796 to about 876, from about 793 to about 879, from about 790 to about 882, from about 787 to about 885, from about 784 to about 888, and from about 781 to about 891 of SEQ ID NO: 40 (Figures 7A-B). In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini, and potentially as many as 10, 20, 30, 40, 50, or 100 nucleotides, at either terminus or at both termini. Such polynucleotide fragments could be used diagnostically to identify individuals, organisms, and/or cells at risk for metabolic, liver, and cardiovascular diseases and/or disorders through the application of such fragments in modern RFLP and SSLP polymorphism analysis. The methodology of such an analysis would readily be apparent to the skilled artisan. Though a few examples are referenced in Methods Mol Biol. 1998;110:1-34, J Clin Lab Anal. 1999;13(5):205-208, and Am. J. Hum. Genet. 44:388-396.

In additional embodiments, the polynucleotides of the invention encode functional attributes of ApoA-IV-L. Preferred embodiments of the invention in this regard include fragments that comprise alpha-helix and alpha-helix forming regions ("alpha-regions"), beta-sheet and beta-sheet forming regions ("beta-regions"), turn and turn-forming regions ("turn-regions"), coil and coil-forming regions ("coil-regions"), hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, flexible regions, surface-forming regions and high antigenic index regions of ApoA-IV-L.

The data representing the structural or functional attributes of ApoA-IV-L set forth in Figure 9 and/or Table 9, as described above, was generated using the various modules and algorithms of the DNA*STAR set on default parameters. In a preferred embodiment, the data presented in columns VIII, IX, XIII, and XIV of Table 9 can be used to determine regions of ApoA-IV-L which exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from the data presented in columns VIII, IX, XIII, and/or XIV by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an environment in which antigen recognition may occur in the process of initiation of an immune response.

Certain preferred regions in these regards are set out in Figure 9, but may, as shown in Table 9, be represented or identified by using tabular representations of the data presented in Figure 9. The DNA*STAR computer algorithm used to generate Figure 9 (set on the original default parameters) was used to present the data in Figure 9 in a tabular format (See Table 9). The tabular format of the data in Figure 9 is used to easily determine specific boundaries of a preferred region.

The above-mentioned preferred regions set out in Figure 9 and in Table 9 include, but are not limited to, regions of the aforementioned types identified by analysis of the amino acid sequence set out in Figure 7A-7B. As set out in Figure 9 and in Table 9, such preferred regions include Garnier-Robson alpha-regions, beta-regions, turn-regions, and coil-regions, Chou-Fasman alpha-regions, beta-regions, and turn-regions, Kyte-Doolittle hydrophilic regions and Hopp-Woods hydrophobic regions, Eisenberg alpha- and beta-amphipathic regions, Karplus-Schulz flexible regions, Jameson-Wolf regions of high antigenic index and Emini surface-forming regions.

Even if deletion of one or more amino acids from the N-terminus of a protein results in modification of loss of one or more biological functions of the protein, other functional activities (e.g., biological activities, ability to multimerize, etc.) may still be retained. For example, the ability of shortened ApoA-IV-L muteins to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptides generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that an ApoA-IV-L mutein with a large number of deleted N-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six ApoA-IV-L amino acid residues may often evoke an immune response.

Accordingly, the present invention further provides polypeptides having one or more residues deleted from the amino terminus of the ApoA-IV-L amino acid sequence shown in Figure 7A-7B, up to the serine residue at position number 361 and polynucleotides encoding such polypeptides. In particular, the present invention

provides polypeptides comprising the amino acid sequence of residues n1-366 of Figure 7A-7B, where n1 is an integer from 2 to 361 corresponding to the position of the amino acid residue in Figure 7A-7B (which is identical to the sequence shown as SEQ ID NO: 212).

In another embodiment, N-terminal deletions of the ApoA-IV-L polypeptide can be described by the general formula n2-361, where n2 is a number from 2 to 361, corresponding to the position of amino acid identified in Figure 7A-7B. N-terminal deletions of the ApoA-IV-L polypeptide of the invention shown as SEQ ID NO: 212 include polypeptides comprising the amino acid sequence of residues: N-terminal deletions of the ApoA-IV-L polypeptide of the invention shown as SEQ ID NO: 212 include polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues: A-2 to P-366; S-3 to P-366; M-4 to P-366;A-5 to P-366; A-6 to P-366; V-7 to P-366; L-8 to P-366; T-9 toP-366; W-10 to P-366; A-11 to P-366; L-12 to P-366; A-13 toP-366; L-14 to P-366; L-15 to P-366; S-16 to P-366; A-17 toP-366; F-18 to P-366; S-19 to P-366; A-20 to P-366; T-21 toP-366; Q-22 to P-366; A-23 to P-366; R-24 to P-366; K-25 toP-366; G-26 to P-366; F-27 to P-366; W-28 to P-366; D-29 toP-366; Y-30 to P-366; F-31 to P-366; S-32 to P-366; Q-33 toP-366; T-34 to P-366; S-35 to P-366; G-36 to P-366; D-37 toP-366; K-38 to P-366; G-39 to P-366; R-40 to P-366; V-41 toP-366; E-42 to P-366; Q-43 to P-366; I-44 to P-366; H-45 toP-366; Q-46 to P-366; Q-47 to P-366; K-48 to P-366; M-49 toP-366; A-50 to P-366; R-51 to P-366; E-52 to P-366; P-53 toP-366; A-54 to P-366; T-55 to P-366; L-56 to P-366; K-57 toP-366; D-58 to P-366; S-59 to P-366; L-60 to P-366; E-61 toP-366; Q-62 to P-366; D-63 to P-366; L-64 to P-366; N-65 toP-366; N-66 to P-366; M-67 to P-366; N-68 to P-366; K-69 toP-366; F-70 to P-366; L-71 to P-366; E-72 to P-366; K-73 toP-366; L-74 to P-366; R-75 to P-366; P-76 to P-366; L-77 toP-366; S-78 to P-366; G-79 to P-366; S-80 to P-366; E-81 toP-366; A-82 to P-366; P-83 to P-366; R-84 to P-366; L-85 toP-366; P-86 to P-366; Q-87 to P-366; D-88 to P-366; P-89 toP-366; V-90 to P-366; G-91 to P-366; M-92 to P-366; R-93 toP-366; R-94 to P-366; Q-95 to P-366; L-96 to P-366; Q-97 toP-366; E-98 to P-366; E-99 to P-366; L-100 to P-366; E-101 toP-366; E-102 to P-366; V-103 to P-366; K-104 to P-366; A-105 toP-366; R-106 to P-366; L-107 to P-366; Q-108 to P-366; P-109 toP-366; Y-110 to P-366; M-111 to P-366; A-112 to P-366; E-113 toP-366; A-114 to P-366; H-115 to P-366; E-

116 to P-366; L-117 toP-366; V-118 to P-366; G-119 to P-366; W-120 to P-366; N-121to P-366; L-122 to P-366; E-123 to P-366; G-124 to P-366; L-125to P-366; R-126 to P-366; Q-127 to P-366; Q-128 to P-366; L-129to P-366; K-130 to P-366; P-131 to P-366; Y-132 to P-366; T-133to P-366; M-134 to P-366; D-135 to P-366; L-136 to P-366;M-137 to P-366; E-138 to P-366; Q-139 to P-366; V-140 to P-366;A-141 to P-366; L-142 to P-366; R-143 to P-366; V-144 to P-366;Q-145 to P-366; E-146 to P-366; L-147 to P-366; Q-148 to P-366;E-149 to P-366; Q-150 to P-366; L-151 to P-366; R-152 to P-366;V-153 to P-366; V-154 to P-366; G-155 to P-366; E-156 to P-366;D-157 to P-366; T-158 to P-366; K-159 to P-366; A-160 to P-366;Q-161 to P-366; L-162 to P-366; L-163 to P-366; G-164 to P-366;G-165 to P-366; V-166 to P-366; D-167 to P-366; E-168 to P-366;A-169 to P-366; W-170 to P-366; A-171 to P-366; L-172 to P-366;L-173 to P-366; Q-174 to P-366; G-175 to P-366; L-176 to P-366;Q-177 to P-366; S-178 to P-366; R-179 to P-366; V-180 to P-366;V-181 to P-366; H-182 to P-366; H-183 to P-366; T-184 to P-366;G-185 to P-366; R-186 to P-366; F-187 to P-366; K-188 to P-366;E-189 to P-366; L-190 to P-366; F-191 to P-366; H-192 to P-366;P-193 to P-366; Y-194 to P-366; A-195 to P-366; E-196 to P-366;S-197 to P-366; L-198 to P-366; V-199 to P-366; S-200 to P-366;G-201 to P-366; I-202 to P-366; G-203 to P-366; R-204 to P-366;H-205 to P-366; V-206 to P-366; Q-207 to P-366; E-208 to P-366;L-209 to P-366; H-210 to P-366; R-211 to P-366; S-212 to P-366;V-213 to P-366; A-214 to P-366; P-215 to P-366; H-216 to P-366;A-217 to P-366; P-218 to P-366; A-219 to P-366; S-220 to P-366;P-221 to P-366; A-222 to P-366; R-223 to P-366; L-224 to P-366;S-225 to P-366; R-226 to P-366; C-227 to P-366; V-228 to P-366;Q-229 to P-366; V-230 to P-366; L-231 to P-366; S-232 to P-366;R-233 to P-366; K-234 to P-366; L-235 to P-366; T-236 to P-366;L-237 to P-366; K-238 to P-366; A-239 to P-366; K-240 to P-366;A-241 to P-366; L-242 to P-366; H-243 to P-366; A-244 to P-366;R-245 to P-366; I-246 to P-366; Q-247 to P-366; Q-248 to P-366;N-249 to P-366; L-250 to P-366; D-251 to P-366; Q-252 to P-366;L-253 to P-366; R-254 to P-366; E-255 to P-366; E-256 to P-366;L-257 to P-366; I-258 to P-366; R-259 to P-366; A-260 to P-366;F-261 to P-366; A-262 to P-366; G-263 to P-366; T-264 to P-366;G-265 to P-366; T-266 to P-366; E-267 to P-366; E-268 to P-366;G-269 to P-366; A-270 to P-366; G-271 to P-366; P-272 to P-366;D-273 to P-366; P-274 to P-366; Q-275 to P-366; M-276 to P-366;L-277 to P-366; S-278 to P-

366; E-279 to P-366; E-280 to P-366;V-281 to P-366; R-282 to P-366; Q-283 to P-366; R-284 to P-366;L-285 to P-366; Q-286 to P-366; A-287 to P-366; F-288 to P-366;R-289 to P-366; Q-290 to P-366; D-291 to P-366; T-292 to P-366;Y-293 to P-366; L-294 to P-366; Q-295 to P-366; I-296 to P-366;A-297 to P-366; A-298 to P-366; F-299 to P-366; T-300 to P-366;R-301 to P-366; A-302 to P-366; I-303 to P-366; D-304 to P-366;Q-305 to P-366; E-306 to P-366; T-307 to P-366; E-308 to P-366;E-309 to P-366; V-310 to P-366; Q-311 to P-366; Q-312 to P-366;Q-313 to P-366; L-314 to P-366; A-315 to P-366; P-316 to P-366;P-317 to P-366; P-318 to P-366; P-319 to P-366; G-320 to P-366;H-321 to P-366; S-322 to P-366; A-323 to P-366; F-324 to P-366;A-325 to P-366; P-326 to P-366; E-327 to P-366; F-328 to P-366;Q-329 to P-366; Q-330 to P-366; T-331 to P-366; D-332 to P-366;S-333 to P-366; G-334 to P-366; K-335 to P-366; V-336 to P-366;L-337 to P-366; S-338 to P-366; K-339 to P-366; L-340 to P-366;Q-341 to P-366; A-342 to P-366; R-343 to P-366; L-344 to P-366;D-345 to P-366; D-346 to P-366; L-347 to P-366; W-348 to P-366;E-349 to P-366; D-350 to P-366; I-351 to P-366; T-352 to P-366;H-353 to P-366; S-354 to P-366; L-355 to P-366; H-356 to P-366;D-357 to P-366; Q-358 to P-366; G-359 to P-366; H-360 to P-366; or S-361 to P-366; of SEQ ID NO: 212. Polypeptides encoded by these polynucleotides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that these bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification or loss of one or more biological functions of the protein, other functional activities (e.g., biological activities (e.g., ability to transport lipids, cholesterol transport, metabolize lipoprotein, etc.), ability to multimerize, and the ability to activate lecithin cholestrol actltransferase may still be retained. For example the ability of the shortened ApoA-IV-L mutein to induce and/or bind to antibodies which recognize the complete or mature forms of the

polypeptide generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that an ApoA-IV-L mutein with a large number of deleted C-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six ApoA-IV-L amino acid residues may often evoke an immune response.

Preferred polypeptides of the invention comprise the following amino acid sequence:

MASMAAVLTWALALLSAFSATQARKGFWDYFSQTSGDKGRVEQIHQQKMA REPATLKDSLEQDLNNMNKFLEKLRPLSGSEAPRLPQDPVGMRRQLQEELEE VKARLQPYMAEAHELVGWNLEGLRQQLKPYTMDLMEQVALRVQELQEQLR VVGEDTKAQLLGGVDEAWALLQGLQSRVVHHTGRFKELFHPYAESLVSGIG RHVQELHRSVAPHAPASPARLSRCVQVLSRKLTLKAKALHARIQQNLDQLRE ELIRAFAGTGTEEGAGPDPQMLSEEVRQRLQAFRQDTYLQIAAFTRAIDQETE EVQQQLAPPPPGHSAFAPEFQQTDSGKVLSKLQARLDDLWEDITHSLHDQGH SHLGDP (SEQ ID NO: 155). Polynucleotides encoding these polypeptides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that these bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

In another embodiment, the polypepitide sequence illustrated in Table I for this gene (SEQ ID NO:96) represents a potential alternative secreted form of the protein. Based upon the location of the start methionine of this polypeptide sequence with respect to the start methionine of the sequence shown in Figures 7A-B (SEQ ID NO: 212), it is unclear which start methionine the cell will utilize during expression.

Thus, both SEQ ID NO: 212 and SEQ ID NO:96 are contemplated by the present invention.

Accordingly, the present invention further provides polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the ApoA-IV-L polypeptide shown in Figure 7A-7B, up to the valine residue at position number 7, and polynucleotides encoding such polypeptides. In particular, the present invention provides polypeptides comprising the amino acid sequence of residues 1-m1 of Figure 7A-7B, where m1 is an integer from 7 to 336 corresponding to the position of the amino acid residue in Figure 7A-7B.

Moreover, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, the amino acid sequence of C-terminal deletions of the ApoA-IV-L polypeptide of the invention shown as SEQ ID NO: 212 (Figures 7A-B) include polypeptides comprising, or alternatively consisting of the amino acid sequence of residues: M-1 to D-365; M-1 to G-364; M-1 toL-363; M-1 to H-362; M-1 to S-361; M-1 to H-360; M-1 to G-359;M-1 to Q-358; M-1 to D-357; M-1 to H-356; M-1 to L-355; M-1 toS-354; M-1 to H-353; M-1 to T-352; M-1 to I-351; M-1 to D-350;M-1 to E-349; M-1 to W-348; M-1 to L-347; M-1 to D-346; M-1 toD-345; M-1 to L-344; M-1 to R-343; M-1 to A-342; M-1 to Q-341;M-1 to L-340; M-1 to K-339; M-1 to S-338; M-1 to L-337; M-1 toV-336; M-1 to K-335; M-1 to G-334; M-1 to S-333; M-1 to D-332;M-1 to T-331; M-1 to Q-330; M-1 to Q-329; M-1 to F-328; M-1 toE-327; M-1 to P-326; M-1 to A-325; M-1 to F-324; M-1 to A-323;M-1 to S-322; M-1 to H-321; M-1 to G-320; M-1 to P-319; M-1 toP-318; M-1 to P-317; M-1 to P-316; M-1 to A-315; M-1 to L-314;M-1 to Q-313; M-1 to Q-312; M-1 to Q-311; M-1 to V-310; M-1 toE-309; M-1 to E-308; M-1 to T-307; M-1 to E-306; M-1 to Q-305;M-1 to D-304; M-1 to I-303; M-1 to A-302; M-1 to R-301; M-1 toT-300; M-1 to F-299; M-1 to A-298; M-1 to A-297; M-1 to I-296;M-1 to Q-295; M-1 to L-294; M-1 to Y-293; M-1 to T-292; M-1 toD-291; M-1 to Q-290; M-1 to R-289; M-1 to F-288; M-1 to A-287;M-1 to Q-286; M-1 to L-285; M-1 to R-284; M-1 to Q-283; M-1 toR-282; M-1 to V-281; M-1 to E-280; M-1 to E-279; M-1 to S-278;M-1 to L-277; M-1 to M-276; M-1 to Q-275; M-1 to P-274; M-1 toD-273; M-1 to P-272; M-1 to G-271; M-1 to A-270; M-1 to G-269;M-1 to E-268; M-1 to E-267; M-1 to T-266; M-1 to G-265; M-1 toT-264; M-1 to G-263; M-1 to A-262; M-1 to F-261; M-1 to A-260;M-1 to R-

259; M-1 to I-258; M-1 to L-257; M-1 to E-256; M-1 toE-255; M-1 to R-254; M-1 to L-253; M-1 to Q-252; M-1 to D-251;M-1 to L-250; M-1 to N-249; M-1 to Q-248; M-1 to Q-247; M-1 toI-246; M-1 to R-245; M-1 to A-244; M-1 to H-243; M-1 to L-242;M-1 to A-241; M-1 to K-240; M-1 to A-239; M-1 to K-238; M-1 toL-237; M-1 to T-236; M-1 to L-235; M-1 to K-234; M-1 to R-233;M-1 to S-232; M-1 to L-231; M-1 to V-230; M-1 to Q-229; M-1 toV-228; M-1 to C-227; M-1 to R-226; M-1 to S-225; M-1 to L-224;M-1 to R-223; M-1 to A-222; M-1 to P-221; M-1 to S-220; M-1 toA-219; M-1 to P-218; M-1 to A-217; M-1 to H-216; M-1 to P-215;M-1 to A-214; M-1 to V-213; M-1 to S-212; M-1 to R-211; M-1 toH-210; M-1 to L-209; M-1 to E-208; M-1 to Q-207; M-1 to V-206;M-1 to H-205; M-1 to R-204; M-1 to G-203; M-1 to I-202; M-1 toG-201; M-1 to S-200; M-1 to V-199; M-1 to L-198; M-1 to S-197;M-1 to E-196; M-1 to A-195; M-1 to Y-194; M-1 to P-193; M-1 toH-192; M-1 to F-191; M-1 to L-190; M-1 to E-189; M-1 to K-188;M-1 to F-187; M-1 to R-186; M-1 to G-185; M-1 to T-184; M-1 toH-183; M-1 to H-182; M-1 to V-181; M-1 to V-180; M-1 to R-179;M-1 to S-178; M-1 to Q-177; M-1 to L-176; M-1 to G-175; M-1 toQ-174; M-1 to L-173; M-1 to L-172; M-1 to A-171; M-1 to W-170;M-1 to A-169; M-1 to E-168; M-1 to D-167; M-1 to V-166; M-1 toG-165; M-1 to G-164; M-1 to L-163; M-1 to L-162; M-1 to Q-161;M-1 to A-160; M-1 to K-159; M-1 to T-158; M-1 to D-157; M-1 toE-156; M-1 to G-155; M-1 to V-154; M-1 to V-153; M-1 to R-152;M-1 to L-151; M-1 to Q-150; M-1 to E-149; M-1 to Q-148; M-1 toL-147; M-1 to E-146; M-1 to Q-145; M-1 to V-144; M-1 to R-143;M-1 to L-142; M-1 to A-141; M-1 to V-140; M-1 to Q-139; M-1 toE-138; M-1 to M-137; M-1 to L-136; M-1 to D-135; M-1 to M-134;M-1 to T-133; M-1 to Y-132; M-1 to P-131; M-1 to K-130; M-1 toL-129; M-1 to Q-128; M-1 to Q-127; M-1 to R-126; M-1 to L-125;M-1 to G-124; M-1 to E-123; M-1 to L-122; M-1 to N-121; M-1 toW-120; M-1 to G-119; M-1 to V-118; M-1 to L-117; M-1 to E-116;M-1 to H-115; M-1 to A-114; M-1 to E-113; M-1 to A-112; M-1 toM-111; M-1 to Y-110; M-1 to P-109; M-1 to Q-108; M-1 to L-107;M-1 to R-106; M-1 to A-105; M-1 to K-104; M-1 to V-103; M-1 toE-102; M-1 to E-101; M-1 to L-100; M-1 to E-99; M-1 to E-98;M-1 to Q-97; M-1 to L-96; M-1 to Q-95; M-1 to R-94; M-1 toR-93; M-1 to M-92; M-1 to G-91; M-1 to V-90; M-1 to P-89; M-1to D-88; M-1 to Q-87; M-1 to P-86; M-1 to L-85; M-1 to R-84;M-1 to P-83; M-1 to A-82; M-1 to E-81; M-1 to S-80; M-1 toG-79; M-1 to S-78; M-1 to L-77; M-1 to P-76; M-1 to R-75; M-1to L-

74; M-1 to K-73; M-1 to E-72; M-1 to L-71; M-1 to F-70; M-1to K-69; M-1 to N-68; M-1 to M-67; M-1 to N-66; M-1 to N-65;M-1 to L-64; M-1 to D-63; M-1 to Q-62; M-1 to E-61; M-1 to L-60;M-1 to S-59; M-1 to D-58; M-1 to K-57; M-1 to L-56; M-1 toT-55; M-1 to A-54; M-1 to P-53; M-1 to E-52; M-1 to R-51; M-1 toA-50; M-1 to M-49; M-1 to K-48; M-1 to Q-47; M-1 to Q-46; M-1to H-45; M-1 to I-44; M-1 to Q-43; M-1 to E-42; M-1 to V-41; M-1to R-40; M-1 to G-39; M-1 to K-38; M-1 to D-37; M-1 to G-36;M-1 to S-35; M-1 to T-34; M-1 to Q-33; M-1 to S-32; M-1 to F-31;M-1 to Y-30; M-1 to D-29; M-1 to W-28; M-1 to F-27; M-1 toG-26; M-1 to K-25; M-1 to R-24; M-1 to A-23; M-1 to Q-22; M-1to T-21; M-1 to A-20; M-1 to S-19; M-1 to F-18; M-1 to A-17; M-1to S-16; M-1 to L-15; M-1 to L-14; M-1 to A-13; M-1 to L-12; M-1to A-11; M-1 to W-10; M-1 to T-9; M-1 to L-8; M-1 to V-7; and M-1 toA-6; of SEQ ID NO: 212. Polypeptides encoded by these polynucleotides are also encompassed by the invention.

Moreover, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, the following amino acid sequences of C-terminal deletions of the mature ApoA-IV-L polypeptide of the invention shown as SEQ ID NO: 212 (Figures 7A-B):

R-24 toD-365; R-24 to G-364; R-24 to L-363; R-24 to H-362; R-24 to S-361; R-24 toH-360; R-24 to G-359; R-24 to Q-358; R-24 to D-357; R-24 to H-356; R-24 toL-355; R-24 to S-354; R-24 to H-353; R-24 to T-352; R-24 to I-351; R-24 toD-350; R-24 to E-349; R-24 to W-348; R-24 to L-347; R-24 to D-346; R-24 toD-345; R-24 to L-344; R-24 to R-343; R-24 to A-342; R-24 to Q-341; R-24 toL-340; R-24 to K-339; R-24 to S-338; R-24 to L-337; R-24 to V-336; R-24 toK-335; R-24 to G-334; R-24 to S-333; R-24 to D-332; R-24 to T-331; R-24 toQ-330; R-24 to Q-329; R-24 to F-328; R-24 to E-327; R-24 to P-326; R-24 toA-325; R-24 to F-324; R-24 to A-323; R-24 to S-322; R-24 to H-321; R-24 toG-320; R-24 to P-319; R-24 to P-318; R-24 to P-317; R-24 to P-316; R-24 toA-315; R-24 to L-314; R-24 to Q-313; R-24 to Q-312; R-24 to Q-311; R-24 toV-310; R-24 to E-309; R-24 to E-308; R-24 to T-307; R-24 to E-306; R-24 toQ-305; R-24 to D-304; R-24 to I-303; R-24 to A-302; R-24 to R-301; R-24 toT-300; R-24 to F-299; R-24 to A-298; R-24 to A-297; R-24 to I-296; R-24 toQ-295; R-24 to L-294; R-24 to Y-293; R-24 to T-292; R-24 to D-291; R-24 toQ-290; R-24 to R-289; R-24 to F-288; R-24 to A-287; R-24 to Q-286; R-24 toL-285; R-24 to R-284;

R-24 to Q-283; R-24 to R-282; R-24 to V-281; R-24 toE-280; R-24 to E-279; R-24 to S-278; R-24 to L-277; R-24 to M-276; R-24 toQ-275; R-24 to P-274; R-24 to D-273; R-24 to P-272; R-24 to G-271; R-24 toA-270; R-24 to G-269; R-24 to E-268; R-24 to E-267; R-24 to T-266; R-24 toG-265; R-24 to T-264; R-24 to G-263; R-24 to A-262; R-24 to F-261; R-24 toA-260; R-24 to R-259; R-24 to I-258; R-24 to L-257; R-24 to E-256; R-24 toE-255; R-24 to R-254; R-24 to L-253; R-24 to Q-252; R-24 to D-251; R-24 toL-250; R-24 to N-249; R-24 to Q-248; R-24 to Q-247; R-24 to I-246; R-24 toR-245; R-24 to A-244; R-24 to H-243; R-24 to L-242; R-24 to A-241; R-24 toK-240; R-24 to A-239; R-24 to K-238; R-24 to L-237; R-24 to T-236; R-24 toL-235; R-24 to K-234; R-24 to R-233; R-24 to S-232; R-24 to L-231; R-24 toV-230; R-24 to Q-229; R-24 to V-228; R-24 to C-227; R-24 to R-226; R-24 toS-225; R-24 to L-224; R-24 to R-223; R-24 to A-222; R-24 to P-221; R-24 toS-220; R-24 to A-219; R-24 to P-218; R-24 to A-217; R-24 to H-216; R-24 toP-215; R-24 to A-214; R-24 to V-213; R-24 to S-212; R-24 to R-211; R-24 toH-210; R-24 to L-209; R-24 to E-208; R-24 to Q-207; R-24 to V-206; R-24 toH-205; R-24 to R-204; R-24 to G-203; R-24 to I-202; R-24 to G-201; R-24 toS-200; R-24 to V-199; R-24 to L-198; R-24 to S-197; R-24 to E-196; R-24 toA-195; R-24 to Y-194; R-24 to P-193; R-24 to H-192; R-24 to F-191; R-24 toL-190; R-24 to E-189; R-24 to K-188; R-24 to F-187; R-24 to R-186; R-24 toG-185; R-24 to T-184; R-24 to H-183; R-24 to H-182; R-24 to V-181; R-24 toV-180; R-24 to R-179; R-24 to S-178; R-24 to Q-177; R-24 to L-176; R-24 toG-175; R-24 to Q-174; R-24 to L-173; R-24 to L-172; R-24 to A-171; R-24 toW-170; R-24 to A-169; R-24 to E-168; R-24 to D-167; R-24 to V-166; R-24 toG-165; R-24 to G-164; R-24 to L-163; R-24 to L-162; R-24 to Q-161; R-24 toA-160; R-24 to K-159; R-24 to T-158; R-24 to D-157; R-24 to E-156; R-24 toG-155; R-24 to V-154; R-24 to V-153; R-24 to R-152; R-24 to L-151; R-24 toQ-150; R-24 to E-149; R-24 to Q-148; R-24 to L-147; R-24 to E-146; R-24 toQ-145; R-24 to V-144; R-24 to R-143; R-24 to L-142; R-24 to A-141; R-24 toV-140; R-24 to Q-139; R-24 to E-138; R-24 to M-137; R-24 to L-136; R-24 toD-135; R-24 to M-134; R-24 to T-133; R-24 to Y-132; R-24 to P-131; R-24 toK-130; R-24 to L-129; R-24 to Q-128; R-24 to Q-127; R-24 to R-126; R-24 toL-125; R-24 to G-124; R-24 to E-123; R-24 to L-122; R-24 to N-121; R-24 toW-120; R-24 to G-119; R-24 to V-118; R-24 to L-117; R-24 to E-116; R-24 toH-115; R-24 to A-114; R-24 to E-113; R-24 to A-112; R-24 to M-111; R-24 toY-110; R-24 to P-109; R-

are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1094 of SEQ ID NO:42, b is an integer of 15 to 1108, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:42, and where b is greater than or equal to a + 14.

24 to Q-108; R-24 to L-107; R-24 to R-106; R-24 toA-105; R-24 to K-104; R-24 to V-103; R-24 to E-102; R-24 to E-101; R-24 toL-100; R-24 to E-99; R-24 to E-98; R-24 to Q-97; R-24 to L-96; R-24 to Q-95;R-24 to R-94; R-24 to R-93; R-24 to M-92; R-24 to G-91; R-24 to V-90; R-24 toP-89; R-24 to D-88; R-24 to Q-87; R-24 to P-86; R-24 to L-85; R-24 to R-84; R-24to P-83; R-24 to A-82; R-24 to E-81; R-24 to S-80; R-24 to G-79; R-24 to S-78;R-24 to L-77; R-24 to P-76; R-24 to R-75; R-24 to L-74; R-24 to K-73; R-24 toE-72; R-24 to L-71; R-24 to F-70; R-24 to K-69; R-24 to N-68; R-24 to M-67; R-24to N-66; R-24 to N-65; R-24 to L-64; R-24 to D-63; R-24 to Q-62; R-24 to E-61;R-24 to L-60; R-24 to S-59; R-24 to D-58; R-24 to K-57; R-24 to L-56; R-24 toT-55; R-24 to A-54; R-24 to P-53; R-24 to E-52; R-24 to R-51; R-24 to A-50; R-24to M-49; R-24 to K-48; R-24 to Q-47; R-24 to Q-46; R-24 to H-45; R-24 to I-44;R-24 to Q-43; R-24 to E-42; R-24 to V-41; R-24 to R-40; R-24 to G-39; R-24 toK-38; R-24 to D-37; R-24 to G-36; R-24 to S-35; R-24 to T-34; R-24 to Q-33; R-24to S-32; R-24 to F-31; R-24 to Y-30; of SEQ ID NO: 212. Polypeptides encoded by these polynucleotides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

In addition, the invention provides nucleic acid molecules having nucleotide sequences related to extensive portions of SEQ ID NO:19 which have been determined from the following related cDNA genes: HLDOE40R (SEQ ID NO:209), HLDOU12R (SEQ ID NO:210), and HLDBC83RA (SEQ ID NO:211).

Based on the sequence similarity to apolipoprotein A-IV of Sus scrofa, the human apolipoprotein A-IV, and the mouse apolipoprotein A-IV, translation product of this gene is expected to share at least some biological activities with apolipoproteins, and specifically apolipoprotein A-IV proteins. Such activities are known in the art, some of which are described elsewhere herein.

Specifically, polynucleotides and polypeptides of the invention are useful for the treatment, detection, and/or prevention of lipid transport & lipoprotein metabolism disorders. Polynucleotides and polypeptides are proposed to be associated with triglyceride-rich lipoproteins & HDL and may play a role in reverse cholesterol transport (cholesterol transport from tissues back to the liver for elimination). Thus, polynucleotides and polypeptides of the invention are useful for treating, detecting, and/or preventing hypercholesterolemia and related disorders. Polynucleotides and polypeptides of the invention are useful for activating lecithin cholesterol acyltransferase and the promotion of cholesterol efflux from cholesterol-preloaded cells. Polymorphisms in apoA-IV are associated with variability in low density lipoprotein (LDL)-cholesterol response to dietary therapy. Moreover, the levels of such polymorphisms (of the 32 currently known to exist in plasma) also appear to correlate with increased incidence and risk for coronary heart diseas. Thus, polynucleotides and polypeptides of the invention are useful for the treatment, detection, and/or prevention of cardiovascular diseases and/or disorders, particularly in the protection against atherogenesis in mice. Polynucleotides and polypeptides of the invention are useful as a satiating factor for controlling appetite and long-term regulation of food intake and body weight (chronic ingestion of a high fat diet blunts apoA-IV response to lipid feeding and may explain why chronic ingestion of a high fat diet predisposes animals and human to obesity).

Polynucleotides and polypeptides of the invention is involved in bile metabolism and is useful in the treatment, detection, and/or prevention of metabolism diseases and/or disorders, particularly for lipid metabolism and lipid emulsification. As inferred above, expression levels and/or polymorphisms in apoA-IV-L may represent diagnostic markers for such conditions as variability in low density lipoprotein (LDL)-cholesterol response to dietary therapy or bile disorders.

Polynucleotides and polypeptides of the invention may represent a diagnostic marker for atherogenesis, atherosclerosis, aberrant cholesteral/LDL/HDL plasma level regulation, obesity, hepatoma, liver diseases and/or disorders, metabolic diseases and/or disorders, obesity, and cardiovascular disease, in general. The full-length protein should be a secreted protein, based upon homology to the apolipoprotein family. Therefore, it is secreted into serum, urine, or feces and thus the levels is

assayable from patient samples. Assuming specific expression levels are reflective of the presence of metabolic dysfunction (e.g., aberrant cholesterol/LDL/HDL levels, bile synthesis dysfunction, lipoprotein metabolism dysfunction, etc.), this would provide a convenient diagnostic for early detection. In addition, expression of this gene product may also be linked to the progression of metabolic disease, and therefore may itself actually represent a therapeutic or therapeutic target for the treatment of cancer.

Therefore, based upon the tissue distribution of this protein in liver, hepatoma, and pancreatic cells and tissues, in combination with its homology to apolipoproteins, indicates that this protein represents a novel, central player in lipid transport and metabolism. Therefore, antagonists directed against this protein is useful in blocking the activity of this protein. Accordingly, preferred are antibodies which specifically bind a portion of the translation product of this gene.

Also provided is a kit for detecting tumors in which expression of this protein occurs. Such a kit comprises in one embodiment an antibody specific for the translation product of this gene bound to a solid support. Also provided is a method of detecting these tumors in an individual which comprises a step of contacting an antibody specific for the translation product of this gene to a bodily fluid from the individual,preferably serum, lymph, urine, seminal fluid, or feces and ascertaining whether antibody binds to an antigen found in the bodily fluid. Preferably the antibody is bound to a solid support and the bodily fluid is serum. The above embodiments, as well as other treatments and diagnostic tests (kits and methods), are more particularly described elsewhere herein.

Polynucleotides and polypeptides of the invention may play an important role in the pathogenesis of human cancers and cellular transformation, particularly those of the gastrointestinal, endocrine, and metabolic systems, and specifically of hepatoma and pancreatic cancers. Polynucleotides and polypeptides of the invention may also be involved in the pathogenesis of developmental abnormalities based upon its potential effects on proliferation and differentiation of cells and tissue cell types. Due to the potential proliferating and differentiating activity of said polynucleotides and polypeptides, the invention is useful as a therapeutic agent in inducing tissue regeneration, for treating inflammatory conditions (e.g., inflammatory bowel

syndrome, diverticulitis, etc.). Moreover, the invention is useful in modulating the immune response to aberrant polypeptides, as may exist in rapidly proliferating cells and tissue cell types, particularly in hepatoma cells, tissues, and other cancers.

The tissue distribution in hepatoma. Liver, and pancreatic cancer indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of metabolic and liver disorders. Representative uses are described in the "Hyperproliferative Disorders", "infectious disease", and "Binding Activity" sections below, in Example 11, and 27, and elsewhere herein. Briefly, the protein can be used for the detection, treatment, and/or prevention of hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells.

Alternatively, the expression within cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA).

Alternatively, this gene product is involved in the pattern of cellular proliferation that accompanies early embryogenesis. Thus, aberrant expression of this gene product in tissues - particularly adult tissues - may correlate with patterns of abnormal cellular proliferation, such as found in various cancers. In addition, other lipocalin family members, specifically cpl1, have been associated with playing a key role in early embryonic development. Through homology, it is expected that polypeptides and polynucleotides of the present invention may also play similar roles. Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore,

the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions.

Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more immunogenic epitopes immunogenic epitopes shown in SEQ ID NO: 111 as residues: Gln-19 to Trp-25, Tyr-27 to Arg-37, His-42 to Glu-49, Asp-55 to Asn-65, Glu-78 to Gln-84, Arg-91 to Glu-98, Glu-120 to Tyr-129, Gln-244 to Arg-251, Glu-265 to Gln-272, Ile-300 to Pro-313, Glu-324 to Gly-331. Polynucleotides encoding said polypeptides are also encompassed by the invention.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:40 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1379 of SEQ ID NO:40, b is an integer of 15 to 1393, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:40, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 31

```
                .         .         .         .         .         .
  1 TGTCCCTTCGTCTCCTTCTTCCCCTAACCAGGCCTCCCTCCACCTGTCTTCTCAGAGCAG   60

                .         .         .         .         .         .
 61 GTAATGGCAAGCATGGCTGCCGTGCTCACCTGGGCTCTGGCTCTTCTTTCAGCGTTTTCG  120
  1   M  A  S  M  A  A  V  L  T  W  A  L  A  L  L  S  A  F  S    19

                .         .         .         .         .         .
121 GCCACCCAGGCACGGAAAGGCTTCTGGGACTACTTCAGCCAGACCAGCGGGGACAAAGGC  180
 20 A  T  Q  A  R  K  G  F  W  D  Y  F  S  Q  T  S  G  D  K  G    39

                .         .         .         .         .         .
181 AGGGTGGAGCAGATCCATCAGCAGAAGATGGCTCGCGAGCCCGCGACCCTGAAAGACAGC  240
 40 R  V  E  Q  I  H  Q  Q  K  M  A  R  E  P  A  T  L  K  D  S    59

                .         .         .         .         .         .
241 CTTGAGCAAGACCTCAACAATATGAACAAGTTCCTGGAAAAGCTGAGGCCTCTGAGTGGG  300
 60 L  E  Q  D  L  N  N  M  N  K  F  L  E  K  L  R  P  L  S  G    79

                .         .         .         .         .         .
301 AGCGAGGCTCCTCGGCTCCCACAGGACCCGGTGGGCATGCGGCGGCAGCTGCAGGAGGAG  360
 80 S  E  A  P  R  L  P  Q  D  P  V  G  M  R  R  Q  L  Q  E  E    99

                .         .         .         .         .         .
361 TTGGAGGAGGTGAAGGCTCGCCTCCAGCCCTACATGGCAGAGGCGCACGAGCTGGTGGGC  420
100 L  E  E  V  K  A  R  L  Q  P  Y  M  A  E  A  H  E  L  V  G   119

                .         .         .         .         .         .
421 TGGAATTTGGAGGGCTTGCGGCAGCAACTGAAGCCCTACACGATGGATCTGATGGAGCAG  480
120 W  N  L  E  G  L  R  Q  Q  L  K  P  Y  T  M  D  L  M  E  Q   139

                .         .         .         .         .         .
481 GTGGCCCTGCGCGTGCAGGAGCTGCAGGAGCAGTTGCGCGTGGTGGGGGAAGACACCAAG  540
140 V  A  L  R  V  Q  E  L  Q  E  Q  L  R  V  V  G  E  D  T  K   159

                .         .         .         .         .         .
541 GCCCAGTTGCTGGGGGGCGTGGACGAGGCTTGGGCTTTGCTGCAGGGACTGCAGAGCCGC  600
160 A  Q  L  L  G  G  V  D  E  A  W  A  L  L  Q  G  L  Q  S  R   179

                .         .         .         .         .         .
601 GTGGTGCACCACACCGGCCGCTTCAAAGAGCTCTTCCACCCATACGCCGAGAGCCTGGTG  660
180 V  V  H  H  T  G  R  F  K  E  L  F  H  P  Y  A  E  S  L  V   199

                .         .         .         .         .         .
661 AGCGGCATCGGGCGCCACGTGCAGGAGCTGCACCGCAGTGTGGCTCCGCACGCCCCCGCC  720
```

FIG. 7A

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200  S  G  I  G  R  H  V  Q  E  L  H  R  S  V  A  P  H  A  P  A    219

721  AGCCCCGCGCGCCTCAGTCGCTGCGTGCAGGTGCTCTCCCGGAAGCTCACGCTCAAGGCC  780
220  S  P  A  R  L  S  R  C  V  Q  V  L  S  R  K  L  T  L  K  A    239

781  AAGGCCCTGCACGCACGCATCCAGCAGAACCTGGACCAGCTGCGCGAAGAGCTTATCAGA  840
240  K  A  L  H  A  R  I  Q  Q  N  L  D  Q  L  R  E  E  L  I  R    259

841  GCCTTTGCAGGCACTGGGACTGAGGAAGGGGCCGGCCCGGACCCCCAGATGCTCTCCGAG  900
260  A  F  A  G  T  G  T  E  E  G  A  G  P  D  P  Q  M  L  S  E    279

901  GAGGTGCGCCAGCGACTTCAGGCTTTCCGCCAGGACACCTACCTGCAGATAGCTGCCTTC  960
280  E  V  R  Q  R  L  Q  A  F  R  Q  D  T  Y  L  Q  I  A  A  F    299

961  ACTCGCGCCATCGACCAGGAGACTGAGGAGGTCCAGCAGCAGCTGGCGCCACCTCCACCA  1020
300  T  R  A  I  D  Q  E  T  E  E  V  Q  Q  Q  L  A  P  P  P  P    319

1021 GGCCACAGTGCCTTCGCCCCAGAGTTTCAACAAACAGACAGTGGCAAGGTTCTGAGCAAG  1080
320  G  H  S  A  F  A  P  E  F  Q  Q  T  D  S  G  K  V  L  S  K    339

1081 CTGCAGGCCCGTCTGGATGACCTGTGGGAAGACATCACTCACAGCCTTCATGACCAGGGC  1140
340  L  Q  A  R  L  D  D  L  W  E  D  I  T  H  S  L  H  D  Q  G    359

1141 CACAGCCATCTGGGGGACCCCTGAGGATCTACCTGCCCAGGCCCATTCCCAGCTCCTTGT  1200
360  H  S  H  L  G  D  P  *                                        367

1201 CTGGGGAGCCTTGGCTCTGAGCCTCTAGCATGGTTCAGTCCTTGAAAGTGGCCTGTTGGG  1260

1261 TGGAGGGTGGAAGGTCCTGTGCAGGACAGGGAGGCCACCAAAGGGGCTGCTGTCTCCTGC  1320

1321 ATATCCAGCCTCCTGCGACTCCCCAATCTGGATGCATTACATTCACCAGGCTTTGCAAAA  1380

1381 AAAAAAAAAAAA  1393
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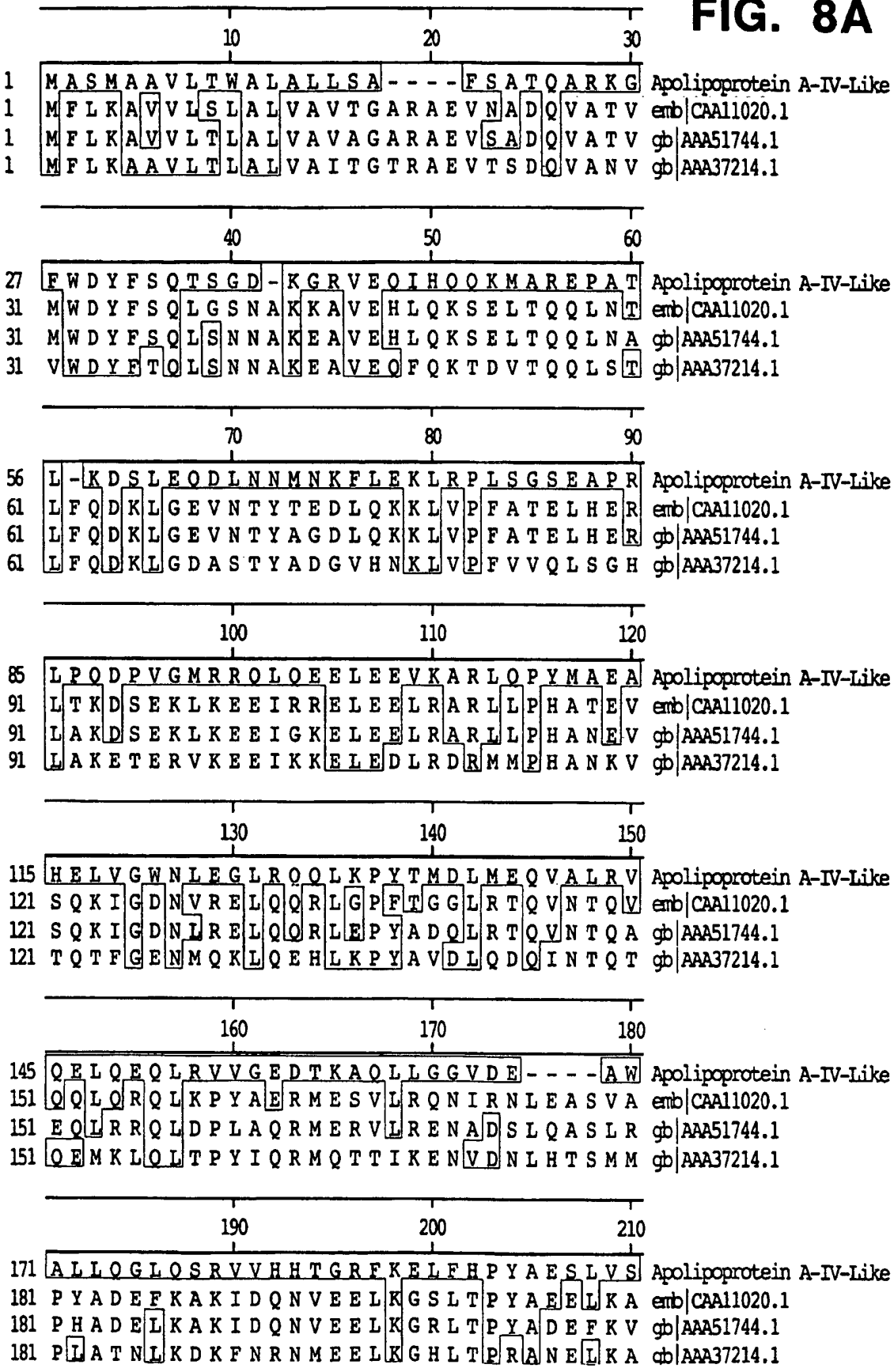
FIG. 7B

FIG. 8A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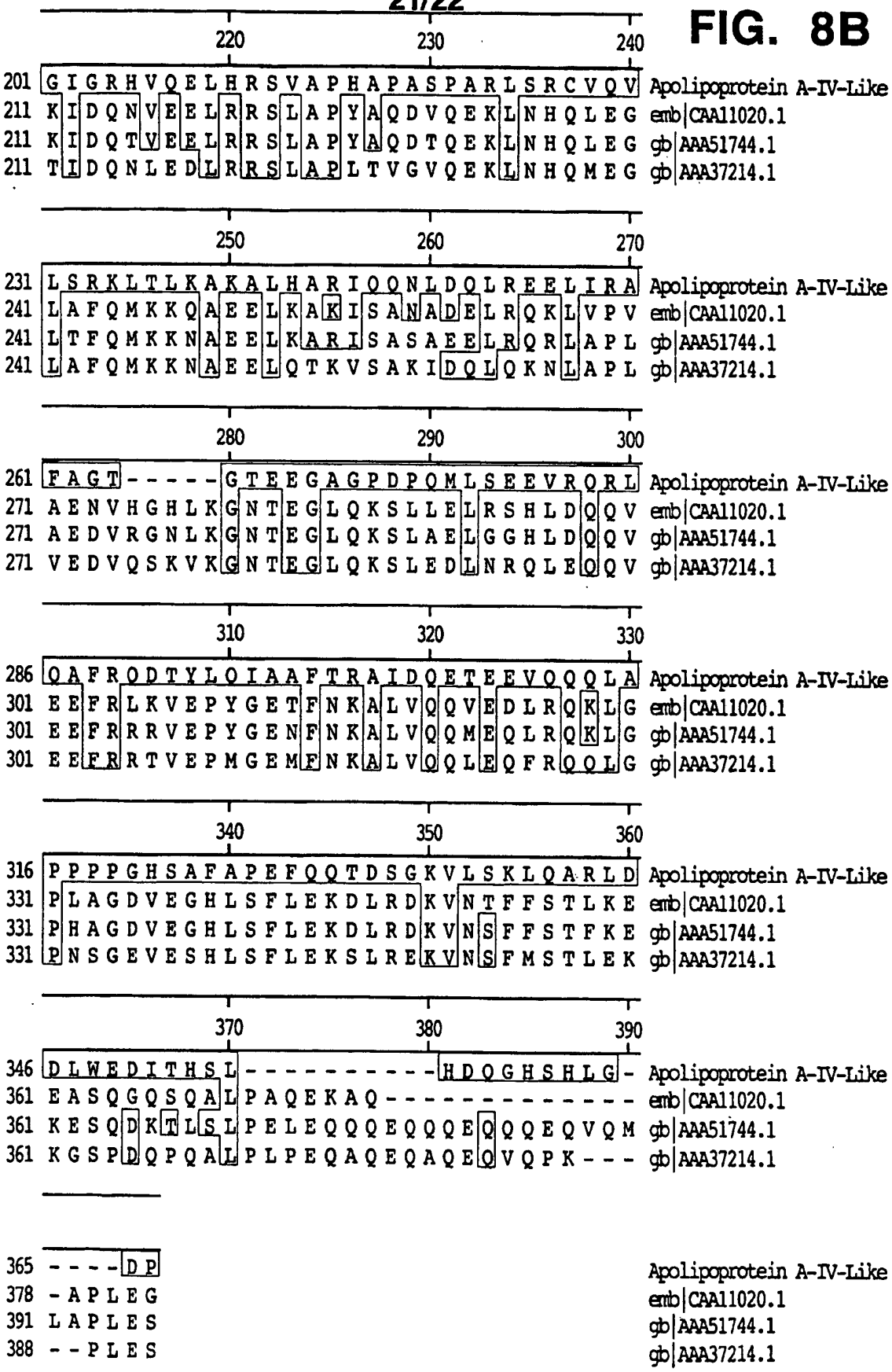
1 MASMAAVLTWALALLSA----FSATQARKG Apolipoprotein A-IV-Like
1 MFLKAVVLSLALVAVTGARAEVNADQVATV emb|CAA11020.1
1 MFLKAVVLTLALVAVAGARAEVSADQVATV gb|AAA51744.1
1 MFLKAAVLTLALVAITGTRAEVTSDQVANV gb|AAA37214.1
40 50 60
27 FWDYFSQTSGD-KGRVEQIHQQKMAREPAT Apolipoprotein A-IV-Like
31 MWDYFSQLGSNAKKAVEHLQKSELTQQLNT emb|CAA11020.1
31 MWDYFSQLSNNAKEAVEHLQKSELTQQLNA gb|AAA51744.1
31 VWDYFTQLSNNAKEAVEQFQKTDVTQQLST gb|AAA37214.1
70 80 90
56 L-KDSLEQDLNNMNKFLEKLRPLSGSEAPR Apolipoprotein A-IV-Like
61 LFQDKLGEVNTYTEDLQKKLVPFATELHER emb|CAA11020.1
61 LFQDKLGEVNTYAGDLQKKLVPFATELHER gb|AAA51744.1
61 LFQDKLGDASTYADGVHNKLVPFVVQLSGH gb|AAA37214.1
100 110 120
85 LPQDPVGMRRQLQEELEEVKARLQPYMAEA Apolipoprotein A-IV-Like
91 LTKDSEKLKEEIRRELEELRARLLPHATEV emb|CAA11020.1
91 LAKDSEKLKEEIGKELEELRARLLPHANEV gb|AAA51744.1
91 LAKETERVKEEIKKELEDLRDRMMPHANKV gb|AAA37214.1
130 140 150
115 HELVGWNLEGLRQQLKPYTMDLMEQVALRV Apolipoprotein A-IV-Like
121 SQKIGDNVRELQQRLGPFTGGLRTQVNTQV emb|CAA11020.1
121 SQKIGDNLRELQQRLEPYADQLRTQVNTQA gb|AAA51744.1
121 TQTFGENMQKLQEHLKPYAVDLQDQINTQT gb|AAA37214.1
160 170 180
145 QELQEQLRVVGEDTKAQLLGGVDE----AW Apolipoprotein A-IV-Like
151 QQLQRQLKPYAERMESVLRQNIRNLEASVA emb|CAA11020.1
151 EQLRRQLDPLAQRMERVLRENADSLQASLR gb|AAA51744.1
151 QEMKLQLTPYIQRMQTTIKENVDNLHTSMM gb|AAA37214.1
190 200 210
171 ALLQGLQSRVVHHTGRFKELFHPYAESLVS Apolipoprotein A-IV-Like
181 PYADEFKAKIDQNVEELKGSLTPYAEELKA emb|CAA11020.1
181 PHADELKAKIDQNVEELKGRLTPYADEFKV gb|AAA51744.1
181 PLATNLKDKFNRNMEELKGHLTPRANELKA gb|AAA37214.1

FIG. 8B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201 G I G R H V Q E L H R S V A P H A P A S P A R L S R C V Q V Apolipoprotein A-IV-Like
211 K I D Q N V E E L R R S L A P Y A Q D V Q E K L N H Q L E G emb|CAA11020.1
211 K I D Q T V E E L R R S L A P Y A Q D T Q E K L N H Q L E G gb|AAA51744.1
211 T I D Q N L E D L R R S L A P L T V G V Q E K L N H Q M E G gb|AAA37214.1
250 260 270
231 L S R K L T L K A K A L H A R I Q Q N L D Q L R E E L I R A Apolipoprotein A-IV-Like
241 L A F Q M K K Q A E E L K A K I S A N A D E L R Q K L V P V emb|CAA11020.1
241 L T F Q M K K N A E E L K A R I S A S A E E L R Q R L A P L gb|AAA51744.1
241 L A F Q M K K N A E E L Q T K V S A K I D Q L Q K N L A P L gb|AAA37214.1
280 290 300
261 F A G T - - - - - G T E E G A G P D P Q M L S E E V R Q R L Apolipoprotein A-IV-Like
271 A E N V H G H L K G N T E G L Q K S L L E L R S H L D Q Q V emb|CAA11020.1
271 A E D V R G N L K G N T E G L Q K S L A E L G G H L D Q Q V gb|AAA51744.1
271 V E D V Q S K V K G N T E G L Q K S L E D L N R Q L E Q Q V gb|AAA37214.1
310 320 330
286 Q A F R Q D T Y L Q I A A F T R A I D Q E T E E V Q Q Q L A Apolipoprotein A-IV-Like
301 E E F R L K V E P Y G E T F N K A L V Q Q V E D L R Q K L G emb|CAA11020.1
301 E E F R R R V E P Y G E N F N K A L V Q Q M E Q L R Q K L G gb|AAA51744.1
301 E E F R R T V E P M G E M F N K A L V Q Q L E Q F R Q Q L G gb|AAA37214.1
340 350 360
316 P P P P G H S A F A P E F Q Q T D S G K V L S K L Q A R L D Apolipoprotein A-IV-Like
331 P L A G D V E G H L S F L E K D L R D K V N T F F S T L K E emb|CAA11020.1
331 P H A G D V E G H L S F L E K D L R D K V N S F F S T F K E gb|AAA51744.1
331 P N S G E V E S H L S F L E K S L R E K V N S F M S T L E K gb|AAA37214.1
370 380 390
346 D L W E D I T H S L - - - - - - - - - - H D Q G H S H L G - Apolipoprotein A-IV-Like
361 E A S Q G Q S Q A L P A Q E K A Q - - - - - - - - - - - - - emb|CAA11020.1
361 K E S Q D K T L S L P E L E Q Q Q E Q Q Q E Q Q Q E Q V Q M gb|AAA51744.1
361 K G S P D Q P Q A L P L P E Q A Q E Q A Q E Q V Q P K - - - gb|AAA37214.1
365 - - - - D P Apolipoprotein A-IV-Like
378 - A P L E G emb|CAA11020.1
391 L A P L E S gb|AAA51744.1
388 - - P L E S gb|AAA37214.1

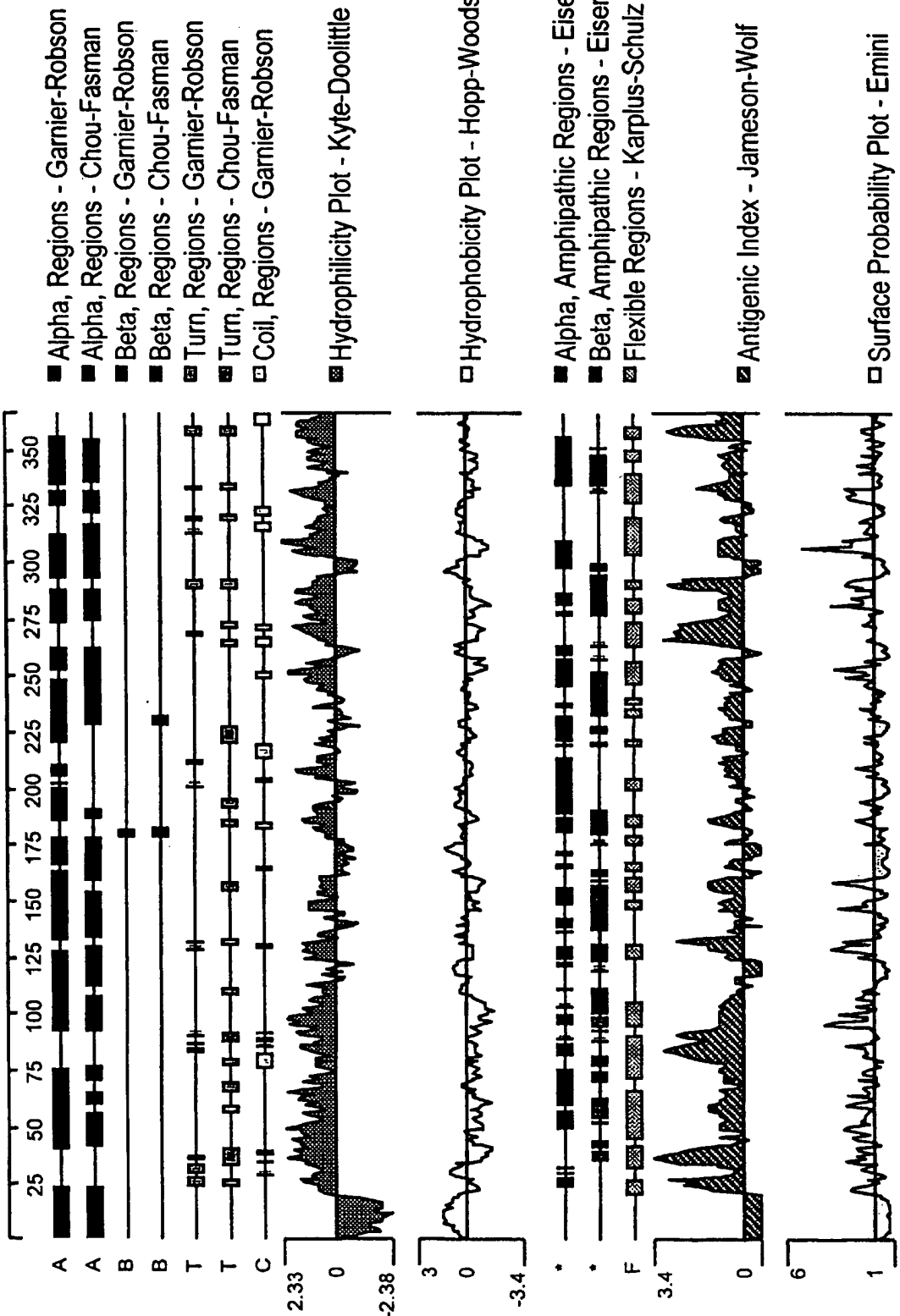
Alpha, Regions - Garnier-Robson
Alpha, Regions - Chou-Fasman
Beta, Regions - Garnier-Robson
Beta, Regions - Chou-Fasman
Turn, Regions - Garnier-Robson
Turn, Regions - Chou-Fasman
Coil, Regions - Garnier-Robson
Hydrophilicity Plot - Kyte-Doolittle
Hydrophobicity Plot - Hopp-Woods
Alpha, Amphipathic Regions - Eisenberg
Beta, Amphipathic Regions - Eisenberg
Flexible Regions - Karplus-Schulz
Antigenic Index - Jameson-Wolf
Surface Probability Plot - Emini
25 50 75 100 125 150 175 200 225 250 275 300 325 350
A A B B T T C
2.33 0 -2.38
3 0 -3.4
* * F
3.4 0
6 1

FIG. 9